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REVIEW

Role of aliskiren in cardio-renal protection and use in hypertensives with multiple risk factors

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Eduardo Pimenta[1]
Suzanne Oparil[2]

[1]Endocrine Hypertension Research Centre and Clinical Centre of Research Excellence in Cardiovascular Disease and Metabolic Disorders, University of Queensland School of Medicine, Greenslopes Princess Alexandra Hospitals, Brisbane, QLD, Australia; [2]Vascular Biology and Hypertension Program, University of Alabama at Birmingham, Birmingham, AL, USA

Abstract: The renin–angiotensin–aldosterone system (RAAS) is a key mediator of blood pressure (BP) and volume regulation in both normotensive and hypertensive persons. Stimulation of RAAS also contributes to hypertension-related target organ damage. The renin–angiotensinogen reaction is the first and rate-limiting step in the generation of angiotensin II (Ang II) and has been a target of antihypertensive drug development for decades. Aliskiren is the first in a new class of orally effective direct renin inhibitors (DRIs) and is approved for the treatment of hypertension in humans. It effectively reduces BP in the general population of hypertensive patients and has a tolerability and safety profile similar to placebo. Aliskiren has favorable effects on vascular inflammation and remodeling, on neurohumoral mediators of various forms of cardiovascular disease, including heart failure, and on proteinuria in diabetic patients. Additional outcome trials are needed to establish the role of this novel class of antihypertensive medication in preventing cardiovascular disease morbidity and mortality.

Keywords: hypertension, renin inhibitors, renin-angiotensin-aldosterone system

Renin–angiotensin–aldosterone system

Blood pressure (BP) and extracellular fluid volume are regulated by the renin–angiotensin–aldosterone system (RAAS) in both normotensive and hypertensive persons. Renin is an aspartyl protease that is synthesized as a preprohormone, cleaved and stored in an inactive (prorenin) form in the juxtaglomerular cells surrounding the afferent arterioles in the kidney.[1] Prorenin is rendered enzymatically active by both proteolytic and nonproteolytic processes. Most proteolytic activation of prorenin occurs within the juxtaglomerular cells by cleavage of its 43 amino acid N-terminal pro-segment.[1] While both prorenin and active renin are secreted from the juxtaglomerular cells into the circulation in response to reductions in glomerular afferent arteriolar pressure, sympathetic nerve stimulation or reduced sodium delivery to the macula densa, prorenin is the predominant circulating form, accounting for approximately 90% of total renin in normal human plasma and for an even greater portion of the total in diabetic patients.[2,3]

Correspondence: Eduardo Pimenta
Hypertension Unit, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD, 4102, Australia
Tel +61 7 3240 5866
Fax +61 7 3240 5031
Email e.pimenta@uq.edu.au

Benefits of the renin–angiotensin–aldosterone system inhibition

Increased RAAS activity, particularly increased angiotensin (Ang) II and aldosterone levels, contribute to target organ damage and enhance cardiovascular risk both by elevating BP and through direct effects on vascular endothelium and cardiac and

renal tissues.[4] Ang II promotes target organ damage through BP elevation and by mediating constriction and remodeling of resistance vessels, aldosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of cathecolamine release from the adrenals and peripheral sympathetic nerve terminals.[5,6]

Various antihypertensive medications, including beta blockers, angiotensin-converting enzyme (ACE) inhibitors, Ang II receptor blockers (ARBs) and aldosterone antagonists, antagonize the RAAS at different steps. RAAS blockers have been used effectively to lower BP, limit or reverse various forms of target organ damage and improve outcomes in patients with hypertension and/or chronic kidney disease, coronary artery disease, left ventricular (LV) hypertrophy and heart failure. Direct renin inhibitors (DRIs), the newest class of antihypertensive agents, block the RAAS at its point of origin, the renin–angiotensinogen reaction, and offer a novel approach to the prevention or reversal of target organ damage and cardiovascular events.[4]

Aliskiren

Aliskiren is the only orally active DRI that has been approved for the treatment of hypertension in humans and has been shown to have favorable effects on target organ damage (Figure 1).[7] Aliskiren is a competitive transition state analog and selective inhibitor of human renin, and has a therapeutic potential similar to that of other antagonists of the RAAS.[8] In humans, the plasma concentration of aliskiren increases dose-dependently after oral administration in doses of 40–640 mg/day, peaking after 3–6 h.[9] The oral bioavailability of aliskiren in humans is limited (2.7%) and the average plasma half-life is 23.7 h, ranging from 20 to 45 h, making aliskiren suitable for once-daily administration.[9] Aliskiren is 47% to 51% protein-bound and the steady-state plasma concentration is reached after 5–8 days of treatment. The main elimination route of aliskiren is via biliary excretion as unmetabolized drug.[9]

Although aliskiren suppresses plasma renin activity (PRA), it causes major reactive increases in plasma renin concentration. This has led some to hypothesize that reactive renin and prorenin secretion may limit the effectiveness of DRIs and can cause target organ damage independent of BP.[10–12] They reason that, if the RAAS is at all leaky, allowing even a small percentage of the excess prorenin generated during DRI treatment to be activated, the antihypertensive effect of the DRI may be offset, limiting its utility as an antihypertensive agent. This theory is controversial and has been questioned.[13] Recently, a study carried out in transgenic mice with selective

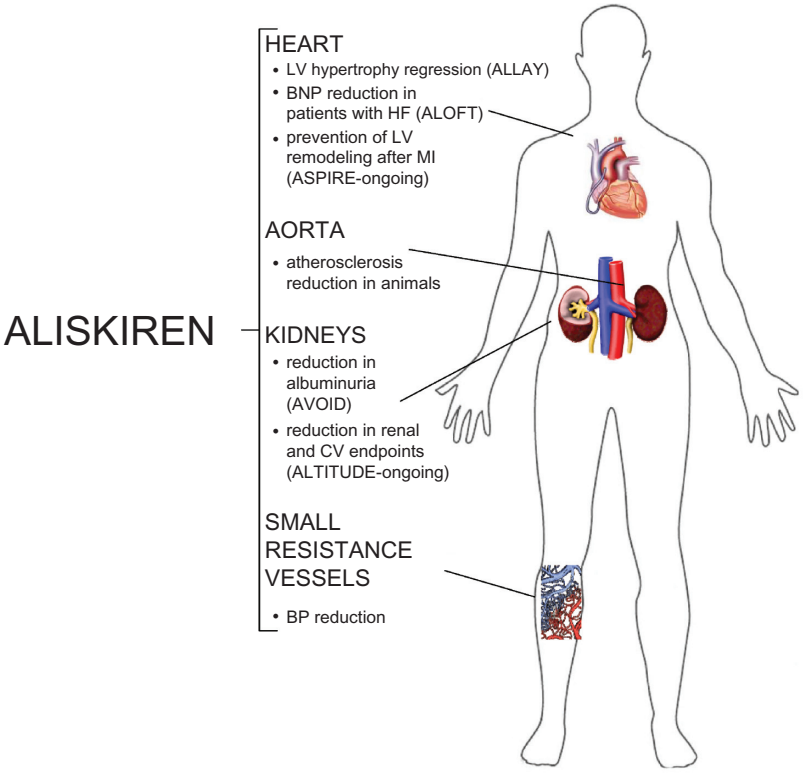

Figure 1 Organs and protective effects demonstrated with aliskiren.
Abbreviations: BNP, B-type natriuretic peptide; BP, blood pressure; CV, cardiovascular; HF, heart failure; LV, left ventricular; MI, myocardial infarction.

increases (13- to 66-fold) in circulating native or active site-mutated prorenin tested the role of prorenin in the tissue remodeling.[14] The primary consequence of chronic elevations in circulating prorenin was high BP without associated increases in cardiac fibrosis or renal glomerular sclerosis.

Aliskiren in the treatment of hypertension

Aliskiren, both as monotherapy and in combination with other agents, has been evaluated extensively in hypertensive patients.[15–17] Aliskiren monotherapy (75–300 mg/day) has a dose-dependent antihypertensive effect that is comparable to that seen with other major classes of antihypertensive drugs and is associated with a placebo level of side effects.[18] Comparator studies have shown that aliskiren is as effective as hydrochlorothiazide (HCTZ), the ARBs irbesartan, losartan, and valsartan, the calcium channel blocker amlodipine and the beta blocker atenolol and may be slightly more effective than ACE inhibitors in lowering BP.[2,19] Further reductions in BP are seen when aliskiren is combined with antihypertensive drugs from the other major classes, including RAAS blockers.[15] Moreover, combination of aliskiren with other antihypertensive agents such as diuretics is a useful strategy in patients who do not respond to aliskiren monotherapy.[20] For example, in one large study that included almost 900 patients, a single-pill combination of aliskiren with HCTZ provided significantly greater BP reduction than aliskiren alone with similar tolerability. Most recently, aliskiren-based therapy (monotherapy ± amlodipine if needed) has been shown to be more effective than HCTZ-based therapy in reducing BP in a study of 1124 hypertensive patients who were followed for one year.[21] Rates of adverse events and laboratory abnormalities with aliskiren treatment are similar to those observed with other RAAS blockers. Furthermore, the combination of aliskiren with ACE inhibitors or ARBs is safe and well tolerated.

Aliskiren in diabetic patients

The RAAS has been implicated in target organ damage in diabetic patients, in whom hypertension is highly prevalent and relatively resistant to treatment, necessitating multiple drug treatment in the majority of cases. The antihypertensive efficacy and safety of aliskiren alone and in combination with the ACE inhibitor ramipril were tested in a double-blind trial carried out in 837 hypertensive diabetic patients.[22] While all therapies produced significant reductions in 24 h ambulatory BP, aliskiren monotherapy was superior to ramipril monotherapy in reducing systolic BP and noninferior in reducing diastolic BP. Importantly, the combination provided an additional mean BP reduction of 4.6/2.1 mmHg over ramipril monotherapy and was well tolerated. These findings suggest that a DRI–ACE inhibitor combination provides an effective and safe therapeutic option for the hypertensive diabetic patient.

Aliskiren in obese patients

Pathophysiologic factors in obesity-related hypertension include both volume expansion and activation of the RAAS. Furthermore, renin may contribute directly to obesity. Transgenic rats overexpressing the human renin gene have been shown to develop moderate obesity with increased body fat mass and glucose intolerance compared with nontransgenic Sprague–Dawley rats.[23] These effects were not reversed by treatment with an ACE inhibitor, a DRI or a (pro)renin receptor blocker, suggesting that the human renin transgene, rather than Ang II, was responsible for the increased appetite, obesity, and metabolic changes seen in this model. The authors point out that these mechanisms are entirely novel and independent of any currently known renin-mediated effects.

To test whether RAAS blockade is a beneficial management strategy in obese hypertensive patients, a randomized double-blind study was carried out in 489 obese (average body mass index [BMI] 34.4 kg/m^2) hypertensive patients that were uncontrolled on HCTZ monotherapy.[24] The study compared the antihypertensive efficacy of aliskiren, irbesartan, amlodipine, and placebo-based treatment added to HCTZ (25 mg). After eight weeks of double-blind treatment, aliskiren/HCTZ produced BP reductions significantly greater than those seen with placebo/HCTZ and similar to those with irbesartan/HCTZ and amlodipine/HCTZ, with similar tolerability to placebo/HCTZ. Adverse event rates were highest with amlodipine/HCTZ because of a higher incidence of peripheral edema. This study demonstrates that combination treatment with aliskiren is an effective and well-tolerated therapeutic option for obese patients with hypertension who fail to achieve BP control with thiazide diuretic treatment, a growing and difficult to manage subgroup of the hypertensive population.

Protective effects of aliskiren

Heart

There is evidence that aliskiren reduces LV hypertrophy as effectively as an ARB. In the Aliskiren Left Ventricular Assessment of Hypertrophy (ALLAY) study, 460 overweight hypertensive patients were randomized to receive

aliskiren, losartan, or a combination of the two.[25] Other antihypertensives could be added as necessary. Aliskiren was noninferior to losartan in reducing LV mass index, but the combination was not superior to losartan alone (Figure 2). These findings suggest that aliskiren is an effective and well-tolerated treatment option for patients with LV hypertrophy. The lack of additional benefit with combination therapy may be related to the design of the study in which there was no significant difference in BP reduction between groups. LV mass reduction seems to be directly related to BP reduction.

Loss of negative feedback inhibition of renin release during chronic treatment with ACE inhibitors leads to a compensatory rise in renin secretion and downstream components of the RAAS cascade, thereby possibly attenuating the benefit of the treatment. Thus, it has been hypothesized that addition of a DRI to chronic ACE inhibitor treatment would benefit patients with heart failure. The Aliskiren Observation of Heart Failure Treatment (ALOFT) study tested this hypothesis in 302 patients with New York Heart Association class II to IV heart failure and plasma brain-type natriuretic peptide (BNP) concentrations >100 pg/mL who were being treated with a beta blocker and an ACE inhibitor or ARB.[26] Compared with placebo treated controls, patients randomized to aliskiren showed significant improvement in neurohormonal profiles, including reductions in PRA, BNP and N-terminal prohormone BNP (NT-proBNP) levels, and in urinary aldosterone concentrations without adverse effects. The findings of ALOFT support further trials to test the safety and efficacy of aliskiren in patients with heart failure, either as an alternative to or in combination with other blockers of the RAAS. However, additional outcome trials are needed to support the benefit of aliskiren in combination with other RAAS blockers in the treatment of heart failure.

Kidneys

The hypothesis that aliskiren can provide renoprotection by reducing albuminuria in patients with diabetes was tested in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study.[27] Specifically, AVOID tested whether dual RAAS blockade achieved by adding aliskiren to the maximal recommended dose of an ARB (losartan) and optimal antihypertensive therapy would reduce albuminuria in 599 patients with hypertension, type 2 diabetes and proteinuria at baseline. Addition of aliskiren to ARB treatment reduced the mean

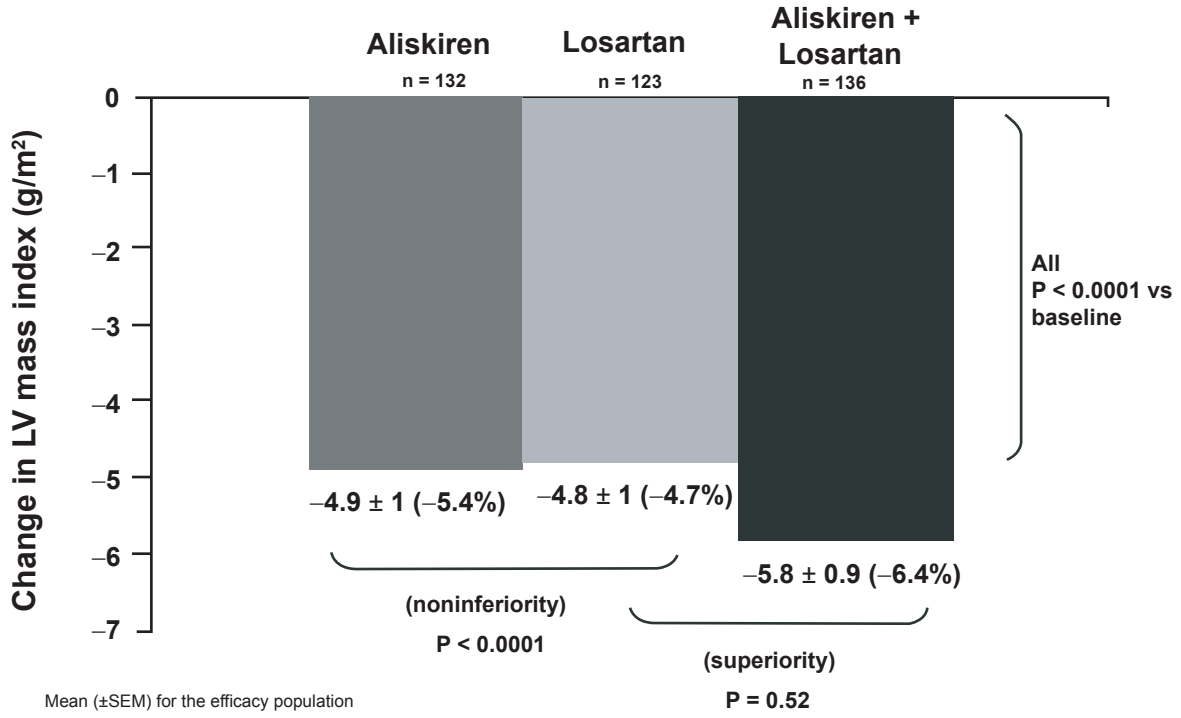

Figure 2 Comparison of left ventricular mass regression in patients receiving aliskiren, losartan, or their combination. Copyright © 2009, American Heart Association. Reproduced with permission from Solomon SD, Appelbaum E, Manning WJ, et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both, on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation*. 2009;119(4):530–7.
Abbreviations: LV, left ventricular; SEM, standard error of mean.

urinary albumin-to-creatinine ratio by 20%, with a reduction of 50% or more in 24.7% of the patients. A nonsignificant 2/1 mmHg difference in BP was seen between the treatment groups, suggesting that the renoprotective effect of aliskiren was independent of BP. Total numbers of adverse and serious adverse events were similar in both groups.

It has been suggested that DRIs may provide more complete and thus more effective blockade of the RAAS than standard recommended treatment with ACE inhibitors or ARBs and, therefore, may be more renoprotective. To test this hypothesis, the response of renal plasma flow (RPF), a measure of intrarenal renin activity, to treatment with aliskiren or an ACE inhibitor (captopril) was measured in 20 healthy normotensive subjects whose RAAS was activated by consumption of a low-sodium diet.[28] The RPF response to aliskiren was maximal at the 600 mg dose (twice the maximal recommended dose for hypertension treatment) and exceeded responses to captopril observed in this study, as well as responses seen previously to both ACE inhibitors and ARBs. Residual vasodilation was observed 48 h after each dose, and aliskiren treatment was associated with significant natriuresis. The authors concluded that DRI treatment provides more complete blockade of the RAAS than treatment with other RAAS blockers and therefore has potential for greater organ protection and improved clinical outcomes, particularly in hypertensive patients with concomitant cardiovascular disease.

Ongoing studies

Ongoing studies are testing whether the DRI aliskiren is effective in prevention or regression of various forms of target organ damage in humans. The Safety and Efficacy of Aliskiren in Post Myocardial Infarction Patients (ASPIRE) is evaluating the efficacy and safety of adding aliskiren to optimized standard therapy in the prevention of LV remodeling in post acute myocardial infarction patients.[29] The Aliskiren Trial in Type 2 Diabetes using Cardiovascular and Renal Disease Endpoints (ALTITUDE) is a placebo controlled trial designed to determine whether adding aliskiren to conventional therapy reduces cardiovascular and renal morbidity and mortality in high risk patients with type 2 diabetes.[30] ALTITUDE is an event driven trial that aims to randomize 8600 patients with type 2 diabetes who are at high risk because of proteinuria, microalbuminuria accompanied by a reduced estimated glomerular filtration rate (eGFR), or a history of cardiovascular disease accompanied by a reduced eGFR with or without microalbuminuria to aliskiren 300 mg daily or placebo added to usual treatment. Multiple cardiovascular and renal endpoints, including death are planned, and the expected follow-up time will be 48 months.

Conclusion

The DRI aliskiren is an effective option in the therapeutic armamentarium of hypertension and related target organ damage. Aliskiren is highly tolerable and safe and also has additive antihypertensive effects when combined with other drug classes. Preliminary studies of the effects of aliskiren on target organ damage such as proteinuria and heart failure demonstrate comparable or greater efficacy compared to other RAAS antagonists.

Disclosure

Dr Pimenta reports no conflicts of interest in this work. Dr Oparil has received grants-in-aid from Abbott Laboratories, Astra Zeneca, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi-Sankyo, Forest Laboratories, GlaxoSmithKline, Novartis, Merck & Co, Pfizer, Sankyo, Sanofi-Aventis, Schering-Plough; has served as consultant for Bristol Myers-Squibb, Daiichi Sankyo, Merck & Co, Novartis, Pfizer, Sanofi Aventis, and The Salt Institute.

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